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US5939312: Miniaturized multi-chamber thermocycler

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Abstract: A miniaturized multi-chamber thermocycler provides a thermocycler which is easy to handle, and permits the treatment of a great number of samples of small sample volumes at high temperature changing rates and at low heating powers. A sample receptacle body manufactured in micro-system technics provides a plurality of sample chambers which are embodied such that at least one of the sample chamber walls of the sample chamber which constitutes the sample chamber base is an efficient heat conductor and also of low mass. Said sample chambers are coupled to a coupling body, serving as heat sink, established via at least one poor heat conducting bridge which, with respect to its dimensioning and/or material selection is such that its specific heat conductance .lambda. is smaller 5 W/K°.multidot.m. The sample chambers are provided with at least one heating element which is constructed to effect, in

CLAIMS: We claim:

[Hide claims]: 1. A miniaturized multi-chamber thermocycler, comprising:

- a sample receptacle mount for receiving fluids, said sample receptacle mount including sample chambers formed therein for receiving said fluids;
- each of said sample chambers being bounded by sample chamber walls including a sample chamber base whereat heat is applied to and removed from said sample chambers, and sampler chamber side walls;
- a coupling support body supporting said sample receptacle mount and functioning as a heat sink;
- said sample receptacle mount including means for coupling said sample chambers to said coupling support body;
- said means for coupling including at least one bridge coupling said sample chambers to said coupling support body and said at least one bridge having a specific heat conductance .lambda. less than 5 W/K.multidot.m to limit heat transfer between said sample chambers and said coupling support body; and
- said sample chamber base including at least one heating element with said sample chamber base functioning as a heat balancing layer.

2. The miniaturized multi-chamber thermocycler as claimed in claim 1, wherein:

- said sample chambers are rectangular with said sample chamber bases being elongated and said side walls include end side walls, opposing one another, which are narrower than an elongate direction of said sample chamber bases;
- said sample chambers are arranged in a row with said elongate direction of said sample chamber base being transverse to said row and said end side walls being disposed at opposing sides of said row; and
- said at least one bridge includes a strip member, formed by etching said sample receptacle mount, extending parallel to said row and adjacent at least one of said end side walls of each of said sample chambers to connect said sample chambers to said coupling support body.

3. The miniaturized multi-chamber thermocycler as claimed in claim 2, further including an insulating bridge member disposed on said strip member and on portions of said sample receptacle mount bordering sides of said strip member.

4. The miniaturized multi-chamber thermocycler as claimed in claim 3, wherein a material of said insulating bridge member is selected from a group of materials consisting of a glass plate, a coating of SiO_2, a coating of $Si_3 N_4$, and coating of a varnish.

5. The miniaturized multi-chamber thermocycler as claimed in claim 2, wherein said at least one heating element is a microstructurized thin layer heater connected to said sample chamber base and having a configuration which provides greater heat at portions of said sample chambers proximate said at least one of said end side walls than at remaining portions of said sample chambers.

6. The miniaturized multi-chamber thermocycler as claimed in claim 3, wherein a material of said sample receptacle mount is silicon.

7. The miniaturized multi-chamber thermocycler as claimed in claim 6, wherein a material of said insulating bridge member is selected from a group of materials consisting of a glass plate, a coating of SiO_2, a coating of $Si_3 N_4$, and coating of a varnish.

8. The miniaturized multi-chamber thermocycler as claimed in claim 6, wherein said sample chambers have a volume in a range of 2 µl to 10 µl.

9. The miniaturized multi-chamber thermocycler as claimed in claim 1, wherein a material of said sample receptacle mount is

- a coupling support body supporting said sample receptacle mount and functioning as a heat sink;
- said sample receptacle mount including means for coupling said sample chambers to said coupling support body;
- said means for coupling including at least one bridge having a specific heat conductance .lambda. less than 5 W/K.multidot.m;
- said sample chambers having at least one heating element;
- said sample receptacle mount having a bottom surface spaced from the coupling support body to define a gap;
- said sample chamber bases forming portions of said bottom surface and being arranged in a common plane; and
- said at least one bridge includes a bridge substance filling said gap between said bottom surface and said coupling support body to connect the sample chambers to the coupling support body.

17. The miniaturized multi-chamber thermocycler as claimed in claim 16, wherein a relationship $.lambda._{sp}/b'_{sp}$ has a value between 300 and 3000 W/K.multidot.m^2, where $.lambda._{sp}$ is a specific heat conductance within said gap and b'_{sp} is a width of said gap.

18. The miniaturized multi-chamber thermocycler as claimed in claim 17, wherein said bridge substance includes at least one material selected from a group consisting of a SiO_2 -plate, a $Si_3 N_4$ -plate and a glass plate.

19. The miniaturized multi-chamber thermocycler as claimed in claim 17, wherein said bridge substance includes one of a fluid and a gaseous medium.

20. The miniaturized multi-chamber thermocycler as claimed in claim 16, wherein said sample bases include said at least one heating element such that said sample chamber bases function as heat balancing layers.

21. The miniaturized multi-chamber thermocycler as claimed in claim 16, wherein a material of said sample receptacle mount is silicon.

22. The miniaturized multi-chamber thermocycler as claimed in claim 21, wherein said sample chambers have a volume in a range of 2 µl to 10 µl.

23. The miniaturized multi-chamber thermocycler as claimed in claim 16, wherein said sample chambers have a volume in a range of2 µl to 10 µl.

24. A miniaturized multi-chamber thermocycler, comprising:

- a sample receptacle mount for receiving fluids, said sample receptacle mount including sample chambers formed therein for receiving said fluids;
- each of said sample chambers being bounded by sample chamber walls including a sample chamber base, whereat heat is applied to and removed from said sample chambers, and sampler chamber side walls;
- a coupling support body supporting said sample receptacle mount;
- said sample receptacle mount including at least one bridge coupling said sample chambers to said coupling support body;
- said sample chamber base including at least one heating element and said sample chamber base functioning as a heat balancing layer;
- said sample chambers being rectangular with said sample chamber bases being elongated and said side walls including end side walls, opposing one another, which are narrower than an elongate direction of said sample chamber bases;
- said sample chambers being arranged in a row with said elongate direction of said sample chamber bases being transverse to said row and said end side walls being disposed at opposing sides of said row;
- said at least one bridge including a strip member, formed by

claim 28, wherein said sample chambers have a volume in a range of 2 μl to 10 μl.

30. A miniaturized multi-chamber thermocycler, comprising:

- a sample receptacle mount for receiving fluids, said sample receptacle mount including sample chambers formed therein for receiving said fluids;
- each of said sample chambers being bounded by sample chamber walls including a sample chamber base, whereat heat is applied to and removed from said sample chambers, and sampler chamber side walls;
- a coupling support body supporting said sample receptacle mount;
- said sample receptacle mount including at least one bridge coupling said sample chambers to said coupling support body so as to thermally insulate said sample chambers from said coupling support body;
- said sample chamber base including at least one heating element and said sample chamber base functioning as a heat balancing layer; and
- said at least one bridge being a strip member formed in said receptacle mount such that said strip member has a thickness less than a thickness of a remainder of said sample receptacle mount surrounding said sample chambers and connects said sample chambers to said coupling support body so as to thermally insulate said sample chambers from said coupling support body.

31. The miniaturized multi-chamber thermocycler as claimed in claim 30, wherein said at least one bridge satisfies a relation G'= (.lambda.$_u$ d_u)/b_{sp}, where G' is a a modified heat conductance having a value between 0.6 and 6 W/K°.multidot.m, .lambda.$_u$ is specific heat conductance of said at least one bridge and is smaller than 5 W/K.multidot.m, d_u is a thickness of said at least one bridge, and b_{sp} is a width of said strip member extending in a direction of a thermal gradient between said sample chambers and said coupling support body.

32. The miniaturized multi-chamber thermocycler as claimed in claim 31, wherein said sample chambers have a volume in a range of 2 μl to 10 μl.

33. The miniaturized multi-chamber thermocycler as claimed in claim 30, wherein said at least one bridge has a specific heat conductance .lambda. less than 5 W/K.multidot.m.

34. The miniaturized multi-chamber thermocycler as claimed in claim 33, wherein said sample chambers have a volume in a range of 2 μl to 10 μl.

Background/Summary:

BACKGROUND OF THE INVENTION

The present invention relates to a miniaturized multi-chamber thermocycler particularly applicable in polymerase chain reaction methods in which desired DNA sequences are amplified, as well as for carrying out other thermally controlled biochemical and biological molecular processes.

Thermally controlled biochemical and biological molecular processes very often involve procedural steps conducted at different temperatures. Such exposure to varying temperatures is particularly applicable to the polymerase chain reaction.

The polymerase chain reaction (PCR) has been recently developed to amplify definite DNA sequences, and its essential features have been outlined, for example, in "Molekulare Zellbiologie", Walter de Gruyter, Berlin-New York 1994, pg. 256/257' by Darnell, J.; Lodish, H.; Baltimore, D. As noted, PCR requires thermal cycling of mixtures of DNA sequences. To this end, stationary sample treatment devices containing reaction chambers are employed into which the respective samples are introduced and then subjected to periodical heating and cooling, the respectively desired DNA sequences being amplified in accordance with the specifically preselected primers contained in the samples.

Presently, PCR is preferably carried out on a plurality of samples

provided a sample receptacle body manufactured in accordance with micro-system techniques, and which comprises a plurality of sample chambers and which provides a defined coupling to a heat sink via at least one poor heat conducting bridge.

Drawing Descriptions:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a lateral section of a part of a first embodiment of the invention;

FIG. 2 is a plan view of an open sample receptacle mount embodied according to FIG. 1;

FIG. 3 is a part of a lateral sectional view of a second embodiment of the invention;

FIG. 4 is a plan view of an alternative embodiment of a sample receptacle mount according to FIG. 3; and

FIG. 5 is one embodiment of a heating element in accordance with the invention.

Description of Preferred Embodiments:

DETAILED DESCRIPTION OF THE INVENTION

Referring to FIG. 1, a miniaturized multi-chamber thermocycler is schematically represented in a lateral section, comprising a sample receptacle mount 1 which has to be a rather good heat conductor. In the example depicted, a silicon wafer is conveniently used as sample receptacle mount 1 in which, by a suitable conventional process of deep-etching, a plurality of properly configured sample chambers 2 are provided such that a sample chamber base 3 thus formed simultaneously provides low mass structure and sufficient heat conductivity. The deep-etching is performed in the region to the right and to the left of sample chamber 2 until only thin strips 5 remain. The width of said strips is designated b_{sp} which is, within the scope of the invention, an essential parameter variably adaptable to the other sample receptacle mount 1 parameters. In the example of FIG. 1, strips 5 are provided with a bridge 7 of poor heat conductivity for which thin glass plates, SiO_2 or $Si_3 N_4$ plates are suited. In addition, coatings made of such materials and deposited in a suitable manner, such as for example varnish, may be used, or corresponding combinations of the aforementioned materials. In the depicted example, pyrex glass plates of about 200 µm thickness are used for bridge 7. The parameters used in the selection and dimensioning are, apart from the strip width b_{sp} which is, for example, 40 µm, the specific heat conductance $.lambda._u$ of the bridge and its thickness du, wherein according to the invention values between about 0.6 and 6 W/K.multidot.m have to be maintained for one relation of the modified heat conductance value $G'=(.lambda._u .multidot.d_u)/b_{sp}$.

In the example disclosed, sample receptacle mount 1 is advantageously formed by assembling two identical partial mounts, manufactured as described hereinabove with regard to sample chamber base 3, in mirror symmetry about an axis designated by dash-lines. It is noted that this is a technologically advantageous embodiment to which the invention is not to be restricted. Other designs of a sample chamber covering are also feasible, for example, those comprised of foils of suitable heat conductivity. The sample chamber base 3 is provided with a heating element 6, 60 which is advantageously a thin-layer heating element attached to the bottom side of the sample chamber base to permit facilitated integration into the manufacturing process. It is also within the intended scope of the invention to provide the sample chamber cover with respective arrangements of heating elements symmetric with sample chamber base 3. Sample chamber base 3 operates as a heat compensation layer, hence, the samples (not shown) insertable into sample chamber 2 are subject to a homogeneous temperature gradient during both heating cycles as well as cooling cycles. The arrangement described is laterally framed by coupling bodies 4, only partially shown, which serve as heat sinks.

In FIG. 2, the arrangement according to FIG. 1 is illustrated schematically and not-to-scale, with the sample chamber cover removed. In practice, at least 96 sample chambers 2 are arranged along silicon wafer receptacle mount 1, the respective narrow sides 8 of which are followed by strips 5 on both sides. The volume of the respective individual sample chambers 2 amounts to, for example,

within a sample only are in an order of size of 5 K. After setting of the thermal balance, the former nearly drops to 0 K. The thermal balance within a sample is achieved in a time period in an order of size of about 10 s.

By virtue of the invention, active temperature control in connection with a low thermal relaxation time of the sample receptacle body, the temperature changing rates are adaptable as desired between about 1 and 15 K/s to the respective conditions of a given PCR experiment.

The features disclosed in the specification, in the subsequent claims, and in the drawings are, individually as well as in any combination, considered as being essential for the invention.

Having described preferred embodiments of the invention with reference to the accompanying drawings, it is to be understood that the invention is not limited to those precise embodiments, and that various changes and modifications may be effected therein by one skilled in the art without departing from the scope or spirit of the invention as defined in the appended claims.

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§ 371 / 102(e) Dates: **1996-12-26** / 1996-12-26

Foreign References:

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EP19930545736A2	European Patent Office (EPO)	6 /1993	
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WO1993WO0022058	World Intellectual Property Organization (WIPO)	11 /1993	
WO1994WO0005414	World Intellectual Property Organization (WIPO)	3 /1994	

Other Abstract Info: CHEMABS 125(17)216343M DERABS C1996-394222

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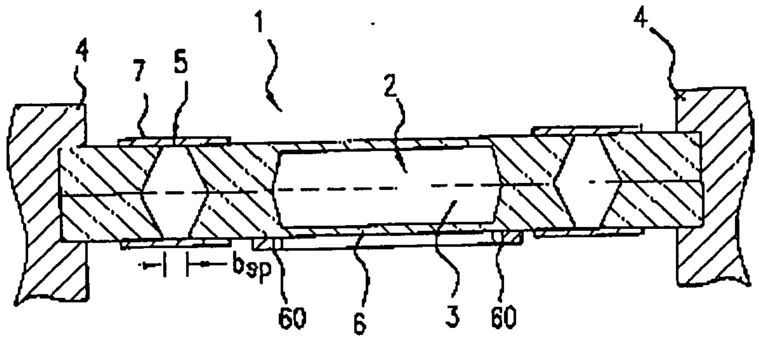

FIG.1

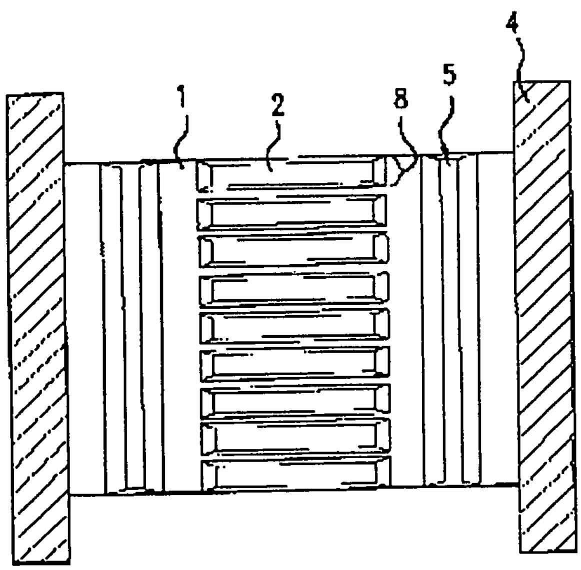

FIG.2

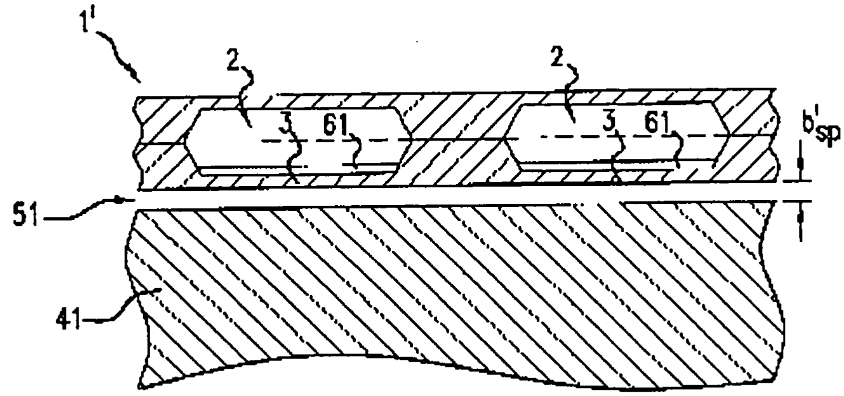

FIG.3

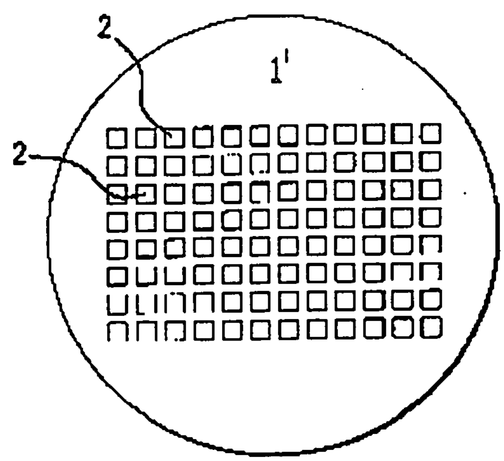

FIG.4

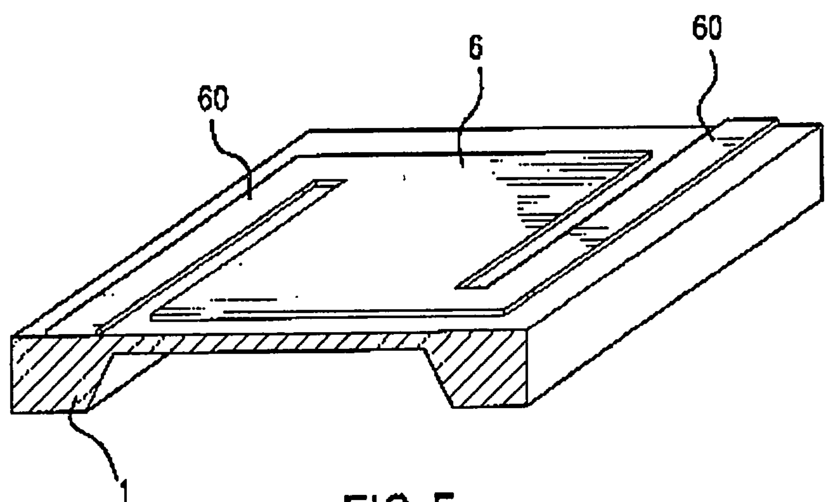

FIG.5